



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 211/22, A61K 31/445		A1	(11) International Publication Number: WO 95/31437
			(43) International Publication Date: 23 November 1995 (23.11.95)
(21) International Application Number: PCT/US95/04942 (22) International Filing Date: 28 April 1995 (28.04.95) (30) Priority Data: 08/245,731 18 May 1994 (18.05.94) US 08/417,161 11 April 1995 (11.04.95) US (71) Applicant: MARION MERRELL DOW INC. [US/US]; 9300 Ward Parkway, Kansas City, MO 64114 (US). (72) Inventors: HENTON, Daniel, R.; 6014 Sturgeon Avenue, Midland, MI 48640 (US). McCARTY, Frederick, J.; 7141 Juniperview Lane, Cincinnati, OH 45243 (US). TRIPP, Susan, I.; 1525 N.E. Yorkshire Drive, Lee's Summit, MO 64086 (US). DeWITT, Jill, E.; 608 West 60th Terrace, Kansas City, MO 64113 (US). (74) Agent: BARNEY, Charlotte, L.; Marion Merrell Dow Inc., 9300 Ward Parkway, Kansas City, MO 64114 (US).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published With international search report.	
(54) Title: PROCESSES FOR PREPARING ANHYDROUS AND HYDRATE FORMS OF ANTIHISTAMINIC PIPERIDINE DERIVATIVES, POLYMORPHS AND PSEUDOMORPHS THEREOF			
<div style="display: flex; justify-content: space-around; align-items: flex-end;"> <div style="text-align: center;"> <p>(I)</p> </div> <div style="text-align: center;"> <p>(II)</p> </div> </div>			
(57) Abstract The present invention is related to novel processes for preparing anhydrous and hydrated forms of piperidine derivatives, polymorphs and pseudomorphs thereof of formulae (I) and (II) which are useful as antihistamines, antiallergic agents and bronchodilators.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

5

10 PROCESSES FOR PREPARING ANHYDROUS AND HYDRATE FORMS OF
 ANTI-HISTAMINIC PIPERIDINE DERIVATIVES, POLYMORPHS AND
 PSEUDOMORPHS THEREOF

15 The present invention is related to novel processes for
preparing anhydrous and hydrated forms of piperidine
derivatives, polymorphs and pseudomorphs thereof which are
useful as antihistamines, antiallergic agents and
bronchodilators [United States Patent No. 4,254,129, March
20 3, 1981, United States Patent No. 4,254,130, March 3, 1981
and United States Patent No. 4,285,958, April 25, 1981].

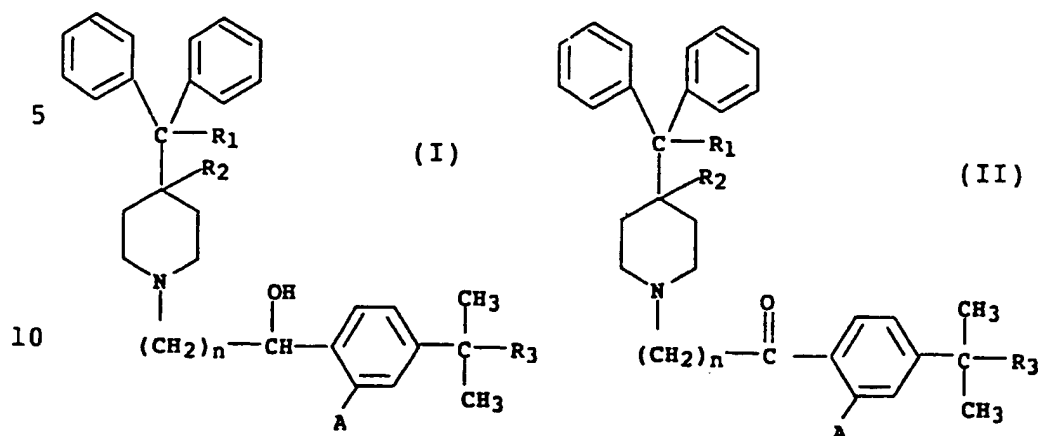
SUMMARY OF THE INVENTION

25 The present invention provides a process for preparing
anhydrous, pharmaceutically acceptable acid addition salts
of piperidine derivatives of the formulas

30

35

-2-

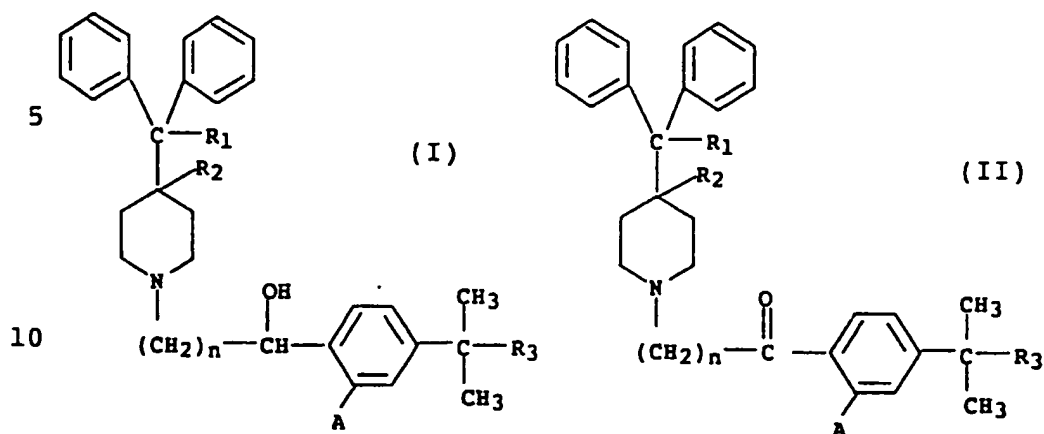


wherein

- 15 R₁ represents hydrogen or hydroxy;
 R₂ represents hydrogen; or
 R₁ and R₂ taken together form a second bond between the
 carbon atoms bearing R₁ and R₂;
 n is an integer of from 1 to 5;
 20 R₃ is -CH₂OH, -COOH or -COOalkyl wherein the alkyl
 moiety has from 1 to 6 carbon atoms and is straight or
 branched;
 each of A is hydrogen or hydroxy; and
 pharmaceutically acceptable salts and individual optical
 25 isomers thereof,
 comprising subjecting the corresponding hydrated,
 pharmaceutically acceptable acid addition salt to an
 azeotropic distillation.

- 30 In addition, the present invention also provides a
 process for preparing anhydrous, pharmaceutically acceptable
 acid addition salts of piperidine derivatives of the formula

35



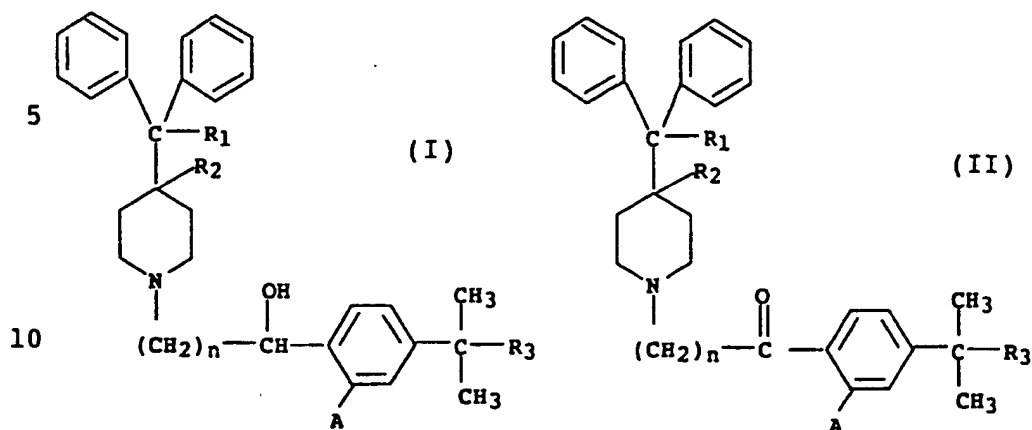
wherein

- 15 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the
carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
20 R_3 is $-CH_2OH$, $-COOH$ or $-COOalkyl$ wherein the alkyl
moiety has from 1 to 6 carbon atoms and is straight or
branched;
each of A is hydrogen or hydroxy; and
pharmaceutically acceptable salts and individual optical
25 isomers thereof,
comprising subjecting the corresponding hydrated,
pharmaceutically acceptable acid addition salt to a water-
minimizing recrystallization.

- 30 In addition, the present invention provides a process
for preparing the hydrated, pharmaceutically acceptable
acid addition salts of piperidine derivatives of the
formula

35

-4-



wherein

- 15 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the
carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
20 R_3 is $-CH_2OH$, $-COOH$ or $-COOalkyl$ wherein the alkyl
moiety has from 1 to 6 carbon atoms and is straight or
branched;
each of A is hydrogen or hydroxy; and
pharmaceutically acceptable salts and individual optical
25 isomers thereof,
comprising subjecting the corresponding anhydrous,
pharmaceutically acceptable acid addition salts to an
aqueous recrystallization.

- 30 In addition, the present invention provides processes
for preparing polymorphs of anhydrous 4-[4-[4-
(Hydroxydiphenylmethyl)-1-piperidinyll]-1-hydroxybutyl]- α,α -
dimethylbenzeneacetic acid hydrochloride designated herein
as Form I and Form III and processes for preparing
35 pseudomorphs of hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-
piperidinyll]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid
hydrochloride designated herein as Form II and Form IV.

The Form I polymorph may be identified by the following characteristics: a visual melting point (capillary tube) in the range of about 196-201°C; a melt endotherm with
5 extrapolated onset in the range of about 195-199°C as determined by differential scanning calorimetry; and an X-ray powder diffraction pattern essentially as shown in Table 1 wherein the XRPD patterns were measured using a powder diffractometer equipped with a Co X-ray tube source. The
10 sample was illuminated with Co K α_1 radiation and XRPD data were collected from 5 to 55° 2 Θ . (intensities may vary radically due to preferred orientation).

Table 1

15	D-Space, Angstroms	Intensity, I/I ₀ , %
	11.8	30
	7.3	30
	6.3	65
20	5.9	35
	5.0	45
	4.8	100
	4.4	45
25	3.9	60
	3.8	75
	3.7	30

30 The Form III polymorph may be identified by the following characteristics: a visual melting point (capillary tube) in the range of about 166-171°C; a broad endotherm below about 90°C, a melt endotherm with an extrapolated
onset of about 166°C as determined by differential scanning
35 calorimetry; and an X-ray powder diffraction pattern essentially as shown in Table 2 wherein the XRPD patterns were measured using a powder diffractometer equipped with a Co X-ray tube source. The sample was illuminated with Co K α_1 radiation and XRPD data were collected from 5 to 55° 2 Θ .

(intensities may vary radically due to preferred orientation).

Table 2

D-Space, Angstroms	Intensity, I/I ₀ , %
9.0	95
4.9	100
4.8	35
4.6	25
4.5	25
3.7	25

15

The Form II pseudomorph may be identified by the following characteristics: a visual melting point (capillary tube) in the range of about 100-105°C; a large broad endotherm below about 100°C and a small endothermic peak (about 2 joules/gram) with extrapolated onsets in the range of about 124-126°C as determined by differential scanning calorimetry; and an X-ray powder diffraction pattern essentially as shown in Table 3 wherein the XRPD patterns were measured using a powder diffractometer equipped with a Co X-ray tube source. The sample was illuminated with Co K α_1 radiation and XRPD data were collected from 5 to 55° 2 Θ . (intensities may vary radically due to preferred orientation).

30

35

-7-

Table 3

	D-Space, Angstr ms	Intensity, I/I ₀ , %
5	7.8	45
	6.4	44
	5.2	85
	4.9	60
	4.7	80
10	4.4	55
	4.2	50
	4.1	60
	3.7	75
15	3.6	60
	3.5	50

The Form IV pseudomorph may be identified by the following characteristics: a visual melting point (capillary tube) in the range of about 113-118°C; two broad overlapping endotherms below about 100°C and an additional endotherm with an extrapolated onset at approximately 146°C as determined by differential scanning calorimetry and an X-ray powder diffraction pattern essentially as shown in Table 4 wherein the XRPD patterns were measured using a powder diffractometer equipped with a Co X-ray tube source. The sample was illuminated with Co K α_1 radiation and XRPD data were collected from 5 to 55° 2 Θ . (intensities may vary radically due to preferred orientation).

Table 4

	D-Space, Angstroms	Intensity, I/I ₀ , %
5	10.4	60
	7.0	45
	6.4	50
	5.3	100
	5.2	55
10	4.3	75
	4.1	50
	4.0	45
	3.8	60
15	3.5	55

DETAILED DESCRIPTION OF THE INVENTION

20

Pharmaceutically acceptable acid addition salts of the compounds of formula (I) and (II), both anhydrous and hydrated, are those of any suitable inorganic or organic acid. Suitable inorganic acids are, for example, hydrochloric, hydrobromic, sulfuric, and phosphoric acids. Suitable organic acids include carboxylic acids, such as, acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, fumaric, malic, tartaric, citric, cyclamic, ascorbic, maleic, hydroxymaleic, and dihydroxymaleic, benzoic, phenylacetic, 4-aminobenzoic, 4-hydroxybenzoic, anthranilic, cinnamic, salicylic, 4-aminosalicylic, 2-phenoxybenzoic, 2-acetoxybenzoic, and mandelic acid, sulfonic acids, such as, methanesulfonic, ethanesulfonic and β -hydroxyethanesulfonic acid.

35

As used herein, the term "hydrate" refers to a combination of water with a compound of formula (I) or (II) wherein the water retains its molecular state as water and

is either absorbed, adsorbed or contained within a crystal lattice of the substrate molecule of formula (I) or (II).

5 As used herein, the term "adsorped" refers to the physical state wherein the water molecule in the hydrated, pharmaceutically acceptable acid addition salts of piperidine derivatives of the formula (I) and (II) is distributed over the surface of the solid hydrated,
10 pharmaceutically acceptable acid addition salts of piperidine derivatives of the formula (I) and (II).

As used herein, the term "absorbed" refers to the physical state wherein the water molecule in the hydrated,
15 pharmaceutically acceptable acid addition salts of piperidine derivatives of the formula (I) and (II) is distributed throughout the body of the solid hydrated, pharmaceutically acceptable acid addition salts of piperidine derivatives of the formula (I) and (II).

20 Hydrated, pharmaceutically acceptable acid addition salts of the compounds of formula (I) and (II) are those hydrates ranging from essentially 0.10 to 5 molecules of water per molecule of substrate salt of formula (I) or
25 (II).

As used herein, the term "azeotropic mixture" refers to a liquid mixture of two or more substances which behaves like a single substance in that the vapor produced by
30 partial evaporation of liquid has the same composition as the liquid. The constant boiling mixture exhibits either a maximum or minimum boiling point as compared with that of other mixtures of the same substance.

35 As used herein, the term "azeotropic distillation" refers to a type of distillation in which a substance is added to the mixture to be separated in order to form an azeotropic mixture with one or more of the constituents of

-10-

the original mixture. The azeotrope or azeotropes thus formed will have boiling points different from the boiling points of the original mixture. As used herein, the term
5 "azeotropic distillation" also refers to co-distillation.

As used herein, the term "water-minimizing recrystallization" refers to a recrystallization wherein the ratio of anhydrous solvent to substrate hydrate is such
10 that the percentage of water present is minimized, thereby inducing precipitation of the anhydrous form of the substrate.

As used herein, the term "aqueous recrystallization"
15 refers to those processes wherein either 1) a solid material is dissolved in a volume of water or a water/organic solvent mixture sufficient to cause dissolution and the solid material recovered by evaporation of the solvent; 2) a solid material is treated with a
20 minimal amount of water or a water/organic solvent mixture which is not sufficient to cause dissolution, heated to obtain dissolution and cooled to induce crystallization or 3) a solid material is dissolved in a volume of water or a water/organic solvent mixture sufficient to cause
25 dissolution and then the solvent is partially evaporated to form a saturated solution which induces crystallization.

As used herein, the term "crystal digestion" refers to that process wherein a solid material is treated with a
30 minimal amount of water or water/organic solvent mixture which is not sufficient to cause dissolution and either heating or stirring at ambient temperature until the desired transformation has taken place.

35 As used herein, the term "antisolvent" refers to a poor solvent for the substance in question which when added to a solution of the substance, causes the substance to precipitate.

-11-

As used herein, the term "suitable temperature" refers to that temperature which is sufficient to cause
5 dissolution and to permit the precipitation of the desired substance either upon addition of an antisolvent or upon removal of the co-solvent by azeotropic distillation.

The anhydrous, pharmaceutically acceptable acid
10 addition salts of piperidine derivatives of the formula (I) and (II) may be prepared from the corresponding hydrated, pharmaceutically acceptable acid addition salts of piperidine derivatives of the formula (I) and (II) by
15 subjecting the corresponding hydrated, pharmaceutically acceptable acid addition salts of piperidine derivatives of the formula (I) and (II) to an azeotropic distillation.

For example, the appropriate hydrated, pharmaceutically acceptable acid addition salt of piperidine derivatives of
20 the formula (I) and (II) is first dissolved in a volume of a suitable solvent or solvent mixture which is sufficient to cause dissolution. Examples of such solvents are water, C₁-C₅ alkanols such as methanol, ethanol and the like; ketone solvents such as acetone, methyl ethyl ketone and
25 the like; aliphatic ester solvents such as ethyl acetate, methyl acetate, methyl formate, ethyl formate, isopropyl acetate and the like and aqueous mixtures of these solvents, such as acetone/water, methyl ethyl ketone/water, water/acetone and water/acetone/ethyl acetate. An
30 additional volume of the same solvent used to effect dissolution or second suitable anhydrous antisolvent is then added to this solution, which is then heated to a boiling point which is suitable to azeotropically remove water and other low boiling components. Suitable anhydrous
35 antisolvents for use in the azeotropic distillation are, for example, ketone solvents such as acetone, methyl ethyl ketone and the like; aliphatic ester solvents such as ethyl acetate, methyl acetate, methyl formate, ethyl formate,

isopropyl acetate and the like; C₅-C₈ aliphatic solvents such as pentane, hexane and the like; aliphatic nitriles, such as acetonitrile and mixtures of these solvents such as acetone/ethyl acetate and the like. The azeotropic mixture of water and solvent is removed by distillation until the temperature changes, indicating that the azeotropic mixture is completely removed. The reaction mixture is cooled and the corresponding anhydrous, pharmaceutically acceptable acid addition salts of piperidine derivatives of the formula (I) and (II) is recovered from the reaction zone by, for example filtration.

In addition, the anhydrous, pharmaceutically acceptable acid addition salts of piperidine derivatives of the formula (I) and (II) may be prepared from the corresponding hydrated, pharmaceutically acceptable acid addition salts of piperidine derivatives of the formula (I) and (II) by subjecting the corresponding hydrated, pharmaceutically acceptable acid addition salts of piperidine derivatives of the formula (I) and (II) to a water-minimizing recrystallization.

For example, the appropriate hydrated, pharmaceutically acceptable acid addition salt of piperidine derivatives of the formula (I) and (II) is dissolved in a volume of a suitable anhydrous solvent or solvent mixture which is sufficient to cause dissolution and heated to reflux. Examples of such solvents are water, C₁-C₅ alkanols such as methanol, ethanol and the like; ketone solvents such as acetone, methyl ethyl ketone and the like; aliphatic ester solvents such as ethyl acetate, methyl acetate, methyl formate, ethyl formate, isopropyl acetate and the like and aqueous mixtures of these solvents, such as acetone/water, methyl ethyl ketone/water, water/acetone and water/acetone/ethyl acetate. An additional volume of the same solvent used to effect dissolution or second suitable anhydrous antisolvent is then added in a quantity

-13-

sufficient to initiate precipitation of the anhydrous, pharmaceutically acceptable acid addition salt of piperidine derivatives of the formula (I) and (II).

- 5 Suitable anhydrous antisolvents are, for example, ketone solvents such as acetone, methyl ethyl ketone and the like; aliphatic ester solvents such as ethyl acetate, methyl acetate, methyl formate, ethyl formate, isopropyl acetate and the like; mixtures of ketone solvents and aliphatic
10 ester solvents such as acetone/ethyl acetate and the like; C₅-C₈ aliphatic solvents such as pentane, hexane and the like; aliphatic nitriles, such as acetonitrile and mixtures of these solvents such as acetone/ethyl acetate and the like as well as mixtures of water and ketone solvents such
15 as acetone/water and the like; and mixtures of water, ketone solvents and aliphatic ester solvents such as acetone/water/ethyl acetate. The reaction mixture is cooled and the corresponding anhydrous, pharmaceutically acceptable acid addition salt of piperidine derivatives of
20 the formula (I) and (II) is recovered from the reaction zone by, for example filtration.

Polymorphic forms of anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -
25 dimethylbenzeneacetic acid hydrochloride (Forms I and III) may be prepared by a variety of methods as detailed below.

Form III to Form I

For example, anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-
30 1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride (Form I) may be prepared from anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride (Form III), by subjecting the anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -
35 dimethylbenzeneacetic acid hydrochloride (Form III) to a crystal digestion as described above.

-14-

Form II to Form III

In addition, anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-
1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic
5 acid hydrochloride (Form III) may be prepared from hydrated
4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-
hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride
(Form II), by subjecting the hydrated 4-[4-[4-
(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -
10 dimethylbenzeneacetic acid hydrochloride (Form II) to water-
minimizing recrystallization as described above.

Form II to Form I

In addition, anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-
15 1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic
acid hydrochloride (Form I) may be prepared from hydrated 4-
[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-
hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride
(Form II), by subjecting the hydrated 4-[4-[4-
20 (Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -
dimethylbenzeneacetic acid hydrochloride (Form II) to water-
minimizing recrystallization as described above or by
subjecting the hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-
piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid
25 hydrochloride (Form II) to an azeotropic distillation.

Form IV to Form I

In addition, anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-
1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic
30 acid hydrochloride (Form I) may be prepared from hydrated 4-
[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-
hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride
(Form IV), by subjecting the hydrated 4-[4-[4-
(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -
35 dimethylbenzeneacetic acid hydrochloride (Form IV) to water-
minimizing recrystallization or to an azeotropic
distillation as described above.

The hydrated, pharmaceutically acceptable acid addition salts of piperidine derivatives of the formula (I) may be prepared from the corresponding compound of the formula (II) wherein R₃ is -COOalkyl by subjecting the corresponding compound of the formula (II) wherein R₃ is -COOalkyl to a reduction using an appropriate reducing agent, such as sodium borohydride, potassium borohydride, sodium cyanoborohydride, or tetramethylammonium borohydride in a suitable solvent, such as, methanol, ethanol, isopropyl alcohol or n-butanol, aqueous mixtures thereof or basic solutions thereof, at temperatures ranging from about 0°C to the reflux temperature of the solvent, and the reaction time varies from about 1/2 hour to 8 hours. After quenching and acidifying with an suitable acid, such as hydrochloric acid, the hydrated, pharmaceutically acceptable acid addition salts of piperidine derivatives of the formula (I) are recovered from the reaction zone by crystallization and filtration.

20

In addition, the hydrated, pharmaceutically acceptable acid addition salts of piperidine derivatives of the formula (I) and (II) may be prepared from the corresponding anhydrous, pharmaceutically acceptable acid addition salts of the formula (I) and (II) by subjecting the corresponding anhydrous, pharmaceutically acceptable acid addition salts of formula (I) and (II) to an aqueous recrystallization.

For example, the appropriate anhydrous, pharmaceutically acceptable acid addition salt of piperidine derivatives of the formula (I) and (II) is treated with a minimal volume of water or suitable water/organic solvent mixture which is insufficient to cause dissolution and heated to reflux. The reaction mixture is cooled and the corresponding hydrated, pharmaceutically acceptable acid addition salt of piperidine derivatives of the formula (I) and (II) is recovered from the reaction zone by, for example

-16-

filtration. Alternatively, the appropriate anhydrous, pharmaceutically acceptable acid addition salt of piperidine derivatives of the formula (I) and (II) is
5 treated with a volume of water or a suitable water/organic solvent mixture which is sufficient to cause dissolution and the water or water/organic solvent is partially or completely evaporated to a volume which induces crystallization of the hydrated, pharmaceutically
10 acceptable acid addition salts of piperidine derivatives of the formula (I) and (II). Suitable solvents for use in the above recrystallization are water, acetone/water, ethanol/water, methyl ethyl ketone/aqueous methanol, methyl ethyl ketone/water and the like.

15

The pseudomorphic forms of hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride (Forms II and IV) may be prepared by a variety of methods as detailed below.

20

Ethyl Ester/Ketone to Form II

Hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride (Form IV) may be prepared from ethyl 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -
25 dimethylbenzeneacetate, hydrochloride or free base as described above for the general preparation of the hydrated, pharmaceutically acceptable acid addition salts of piperidine derivatives of the formula (I) from the
30 corresponding compound of the formula (II) wherein R_3 is -COOalkyl, but rapidly adding water over a period of time ranging from 1 minute to 45 minutes at a temperature range of about -20°C to 50°C to precipitate the hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -
35 dimethylbenzeneacetic acid hydrochloride (Form II).

Ethyl Ester/Ketone to Form IV

-17-

Hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride (Form IV) may be prepared from ethyl 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylbenzeneacetate, hydrochloride or free base as described above for the general preparation of the hydrated, pharmaceutically acceptable acid addition salts of piperidine derivatives of the formula (I) from the corresponding compound of the formula (II) wherein R₃ is -COOalkyl, but slowly adding water over a period of time ranging from about 30 minutes to 24 hours and at a temperature range of about 0°C to 50°C, optionally with seeding, to precipitate the hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride (Form IV).

Form I to Form II

Hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride (Form II) may be prepared from anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride (Form I) by subjecting hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride (Form II) to an aqueous recrystallization as defined above.

Starting materials for use in the present invention are readily available to one of ordinary skill in the art. For example, ethyl 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylbenzeneacetate, hydrochloride is described in U.S. Patent 4,254,129, March 3, 1981.

35

The following examples present typical processes for preparing the anhydrous and hydrated, pharmaceutically acceptable acid addition salts of piperidine derivatives of

-18-

the formula (I) and (II), polymorphs and pseudomorphs thereof. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the following terms have the indicated meanings: "g" refers to grams; "mol" refers to mole; "mmol" refers to millimoles; "mL" refers to milliliters; "bp" refers to boiling point; "mp" refers to melting point; "°C" refers to degrees Celsius; "mm Hg" refers to millimeters of mercury; "μL" refers to microliters; "μg" refers to micrograms; and "μM" refers to micromolar.

Differential Scanning Calorimetry analysis were performed using a TA 2910 DSC with open aluminum pans. The samples were heated to 240°C at 5°C/minute with a 50mL/minute nitrogen purge.

X-Ray Powder Diffraction analyses were performed as follows:

The samples were loaded into a quartz (zero scatter) sample holder for the XRPD pattern measurement. The XRPD patterns were measured using a powder diffractometer equipped with a Co X-ray tube source, primary beam monochromator, and position sensitive detector (PSD). The incident beam was collimated using a 1° divergence slit. The active area on the PSD subtended approximately $5^{\circ}2\theta$. The source was operated at 35 kV and 30 mA and the sample was illuminated with Co $K\alpha_1$ radiation. XRPD data were collected from 5 to $55^{\circ}2\theta$ at a rate of $0.25^{\circ}2\theta$ /minute and a step width of $0.02^{\circ}2\theta$. The XRPD patterns were measured without the addition of an internal calibrant.

Peak positions and intensities for the most prominent features were measured using a double-derivative peak picking method. X-ray peaks with I/I_0 greater than 20% were reported. The cutoff was chosen arbitrarily. The

-19-

intensities are rounded to the nearest 5%. Certain peaks appear sensitive to preferred orientation that is caused by changes in crystallite morphology. This results in large
5 changes in the I/I_0 value.

Example 1-Preparation of Form II

4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride

10 Method A

Mix ethyl 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylbenzeneacetate, hydrochloride (101.92g, 0.1807mol) and methanol (510mL) and stir. Rapidly add 50% sodium hydroxide (72.27g, 0.903mol) and
15 wash in with water (61mL). Heat to reflux for 2 hours, allow to cool to 35°C and treat with sodium borohydride (3.42g, 0.0903mol). Add water (100mL) and maintain at 35°C for 10 hours. Add 37% hydrochloric acid (53.0g) to adjust pH to 11.5. Add acetone (26.5mL) and water (102mL). Hold
20 at 35°C for 2 hours and adjust to pH 2.5 with 37% hydrochloric acid (44.69g). Dilute with water (408mL), cool to -15°C, stir for 1.5 hours and collect the precipitate by vacuum filtration. Wash the filtercake with deionized water (3X100mL) and vacuum dry to give 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -
25 dimethylbenzeneacetic acid hydrochloride hydrate (97.10g).

Method B

Place ethyl 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylbenzeneacetate, hydrochloride
30 (60.01g, 0.106mol) in a 1-L three necked round-bottom flask and fit the flask with a mechanical stirrer, a Claisen head, a thermometer and a reflux condenser with a nitrogen bubbler on top. Add methanol (300mL) and turn the stirrer
35 on. Dilute the slurry with water (60mL) and heat to 52-54°C over 15-20 minutes. Hold at 52°C for 2 hours and then add 50% sodium hydroxide (42.54g, 0.532mol). Heat at 73 C for approximately 1 hour, 45 minutes, cool to less than 35°C

-20-

using a water bath and then add sodium borohydride (2.02g, 0.0534mol). Stir overnight at 35°C, treat with acetone (15.5 mL) and stir for 2 hours at 35°C. Acidify the mixture
5 to a pH of 1.85 with 28% hydrochloric acid (75.72g), dilute with water (282 mL), stir for about 30 minutes and cool over about 2 hours to -15°C. Filter the solids off and wash with water (2X75mL) and ethyl acetate (2X75mL). Vacuum dry the solid and allow to stand for 2 days to give 4-[4-[4-
10 (hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride hydrate (Form II) (57.97g, 91.5%) as a fine powder.

Method C

15 Place ethyl 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylbenzeneacetate (56.12g, 0.1064mol) in a 1-L three necked round-bottom flask and fit the flask with a mechanical stirrer, a Claisen head, a thermometer and a reflux condenser with a nitrogen bubbler on top. Add
20 methanol (300mL) and turn the stirrer on. Dilute the slurry with water (60mL) and heat to reflux using a heating mantle controlled by a Therm-O-Watch. When the mixture reaches about 35°C, treat with 50% sodium hydroxide (34.05g, 0.4256mol) and rinse in with water (42mL). Stir at reflux
25 for 2 hours, 15 minutes, cool over 1 hour to 35°C and then treat with sodium borohydride (2.02g, 0.0534mol). Stir for 7.5 hours and allow to stand at room temperature without stirring for 1.75 days. Warm the mixture to 35°C and quench with acetone (15.5mL, 0.21mol) and stir for 2 hours. Add
30 water (60mL) and adjust the pH to 2.5 with 32% hydrochloric acid (65.22g). Cool to 40°C and rinse the pH probe with water (25mL). Add water over about 30 minutes (192mL), hold the temperature at 33°C for 10 minutes and add a few seed crystals. Cool the slurry to -12°C over about 45
35 minutes and isolate the solid by filtration (586.2g). Wash with water (2X100mL) and then with ethyl acetate (100mL, prechilled to about -10°C). Vacuum dry overnight (1 mmHg, 50 C) to give 4-[4-[4-(hydroxydiphenylmethyl)-1-

-21-

piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride hydrate (Form II) (58.86g, 98%) as a white solid.

5

Example 2-Preparation of Form IV

4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride (Form IV)

- 10 Place ethyl 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylbenzeneacetate (56.12g, 0.1064mol) in a 1-L three necked round-bottom flask and fit the flask with a mechanical stirrer, a Claisen head, a thermometer and a reflux condenser with a nitrogen bubbler on top. Add
- 15 methanol (300mL) and turn the stirrer on. Dilute the slurry with water (60mL) and heat to reflux using a heating mantle controlled by a Therm-O-Watch. When the mixture reaches about 35°C, treat with 50% sodium hydroxide (34.05g, 0.4256mol) and rinse in with water (42mL). Stir at reflux
- 20 for 2 hours, 15 minutes, cool over 1 hour to 35°C and then treat with sodium borohydride (2.02g, 0.0534mol). Stir for 7.5 hours and allow to stand at room temperature without stirring for 1.75 days. Warm the mixture to 35°C and quench with acetone (15.5mL, 0.21mol) and stir for 2 hours. Add
- 25 water (60mL) and adjust the pH to 2.5 with 32% hydrochloric acid (65.22g). Cool to 40°C and rinse the pH probe with water (25mL). Hold the temperature at 33°C for 10 minutes, add a few seed crystals and add water over about 4 hours (192mL) at 35°C. Cool the slurry to -12°C over about 45
- 30 minutes and isolate the solid by filtration (586.2g). Wash with water (2X100mL) and then with ethyl acetate (100mL, prechilled to about -10°C). Vacuum dry overnight (1 mmHg, 50°C) to give 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid
- 35 hydrochloride hydrate (Form IV); mp 115-116°C (dec).

XRPD: Table 5

Table 5

	D-Space, Angstroms	Intensity, I/I ₀ , %
5	10.38	60
	6.97	45
	6.41	50
	5.55	30
10	5.32	100
	5.23	55
	5.11	35
	4.98	25
	4.64	30
15	4.32	35
	4.28	75
	4.12	50
	4.02	45
20	3.83	60
	3.65	20
	3.51	55
	3.46	25
25	2.83	20

Example 3-Conversion of Form II to Form I

4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride (Form I)

Treat 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride hydrate (Form II) (20.0g, 0.0355mol) with deionized water (2g) and add acetone (60mL) in small portions over several minutes with stirring. Filter through filter aid and wash the filter cake with acetone (30mL). Wash the filtercake with acetone (22mL), reflux filtrate and then slowly add ethyl acetate (32mL over 15 minutes) keeping the mixture at

-23-

reflux. Reflux for 10 minutes, then slowly add additional ethyl acetate (23mL over 10 minutes) and reflux for an additional 15 minutes. Add additional ethyl acetate (60mL over 5-10 minutes) and continue refluxing for 15 minutes. Cool to approximately 8°C in an ice bath, filter the solid and wash with ethyl acetate (85mL). Vacuum dry at 55°C for 1.5 hours to give the title compound (18.16g, 95%).

10 Example 4-Conversion of Form II to Form I
4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride

Method A:

15 Treat 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride hydrate (Form II) (5.00g, 0.0083mol) with methylethyl ketone (130mL). Slowly add water (0.4mL), filter through filter aid and wash the filter cake with methylethyl ketone (20mL). Heat to reflux and distill off 75mL of solvent, cool to -15°C and collect by vacuum filtration. Wash with methylethyl ketone (2X10mL) and vacuum dry at 60°C to give the title compound (4.33g, 97%); mp 196-198°C.

25 Method B:

Treat 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride hydrate (Form II) (1.4g) with acetone (60mL) and heat to reflux. Reduce the volume to approximately 35mL to remove all water which boils off as an azeotrope (88/12:acetone/water). Cool the solution and collect the title compound as a crystalline solid.

Method C:

35 Mix 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride hydrate (Form II) (53.88g, 0.100mol) and add water (4.79g) and methyl ethyl ketone (240mL). Stir until the solid is

-24-

slurried up and add additional methyl ethyl ketone (1L). Stir for 0.5 hours, filter through a pad of filter aid, wash the filtercake with methyl ethyl ketone (100mL) and transfer the filtrate and wash to a 2L, 3-necked flask fitted with a thermometer, mechanical stirrer and distillation head. Distill off a total of 721mL of methyl ethyl ketone, cool and stir over 1 hour to 40°C. Cool to -15°C and hold for 10 minutes. Collect the solid by vacuum filtration and wash the filtercake with methyl ethyl ketone (2X65mL) and vacuum dry at 55°C overnight to give the title compound (52.76g, 97.9%); mp 197.5-200°C.

Method D:

15 Treat 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride hydrate (Form II) (40.0g, 0.0696mol, assayed at 93.6% purity, having 0.89g water present and 35.1g, 0.0575mol, assayed at 88.0% purity, having 2.47g water present) with water (8.30g; the amount calculated to bring the weight of water present to 17% of the anhydrous weight of 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride hydrate, taking into account the water in the hydrated salt). Add methyl ethyl ketone (approximately 500mL) and stir until most of the solids dissolve. Add additional methyl ethyl ketone (700mL) in portions over approximately 10 minutes and continue stirring for 1/2 hour. Filter through a thin pad of filter aid, wash the filtercake and flask with additional methyl ethyl ketone (100mL) and transfer to a boiling flask fitted with a thermometer, mechanical stirrer, heating mantle, a 12-plate Oldershaw (vacuum-jacketed) distillation column and a distillation head with the capability of regulating the reflux ratio in a rough fashion, washing in with additional methyl ethyl ketone (100mL). Distill off 450 mL of solvent, cool to -15°C and filter the solid. Wash with methyl ethyl ketone (2X100mL)

-25-

and dry to give the title compound (68.3g, 99.9%); mp 197-199°C.

5 Method E

Bring methyl ethyl ketone (4mL) to a boil and add 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride (500mg). Decant the top layer and add methyl ethyl ketone (3mL) to the aqueous layer. Boil the solution until the temperature reached 79°C, reduce the volume by 25%, remove from heat and cover with aluminum foil. Allow the solution to cool, filter the resulting crystals and air dry to give the title compound.

15

Example 5-Conversion of Form I to Form II

4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride hydrate

20

Method A

Treat 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride (Form I) (2.0g) with ethanol (4mL) and deionized water (20mL). Heat at 80°C until a solution is formed and then stir at room temperature for 23 hours. Filter the resulting slurry, wash with water (2X10mL) and dry under vacuum at 35°C overnight to give the title compound (1.88g); mp 100-105°C.

30

XRPD: Table 6

35

Table 6

	D-Space, Angstroms	Intensity, I/I ₀ , %
5	11.41	20
	7.98	20
	7.83	45
	6.58	45
10	6.42	60
	5.66	20
	5.52	45
	5.39	30
	5.23	65
15	5.14	45
	4.86	65
	4.72	100
	4.45	65
20	4.40	45
	4.32	45
	4.18	45
	4.06	65
	4.02	55
25	3.85	25
	3.79	75
	3.74	95
	3.61	80
30	3.56	25
	3.47	65
	3.41	20
	2.74	20

-27-

Method B

Mix water (35.5mL), methanol (26.3mL) and sodium chloride
5 (2.59g). Add 4-[4-[4-(hydroxydiphenylmethyl)-1-
piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid
hydrochloride (Form I) (4.77g). Heat to reflux on a steam
bath until dissolution and cool to -10°C . Filter the
resulting solid, wash with water (2X25mL) and vacuum dry
10 overnight to give the title compound (4.80g).

Example 6-Conversion of Form II into Form III

4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-
hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride
15 (Form III)

Place 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-
hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride
hydrate (Form II) (55.56g, 0.0929mol having 10% water) in a
20 pressure bottle along with water (2.96g) and acetone
(38.1g). Seal the bottle tightly and heat to approximately
 80°C . Cool to about 50°C , filter through filter aid in a
coarse sintered glass funnel and dilute with acetone (90g).
Transfer to a 1L flask fitted with a mechanical stirrer,
25 thermometer and a reflux condenser. Heat the mixture to
reflux and allow to cool and stir over the weekend. Cool
to -15°C and filter on a coarse sintered glass funnel, wash
with ethyl acetate (2X50mL) and vacuum dry at 50°C .

30 Place a majority of the solid obtained (45.24g) in a 500 mL
three necked flask fitted with a mechanical stirrer,
thermometer and a reflux condenser. Add acetone (240mL)
and water (4.82g) and reflux the mixture overnight. Allow
the slurry to cool to 35°C and place in an ice water bath
35 and cool to less than 5°C . Filter the solid off on a coarse
sintered glass funnel, wash with ethyl acetate (50mL) and
vacuum dry at 50°C for several hours to give the title

-28-

compound as a white crystalline powder (43.83g, 97%); mp 166.5-170.5°C.

5 XRPD: Table 7

Table 7

	D-Space, Angstroms	Intensity, I/I ₀ , %
10	8.95	95
	4.99	20
	4.88	100
	4.75	35
	4.57	25
15	4.47	25
	4.46	20
	3.67	20
	3.65	25

20

Example 7-Conversion of Form III into Form I

4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride
25 (Form I)

Place 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride (Form III) (40.0g as an ethyl acetate wetcake-27.9g dry basis) in a 1L three necked flask fitted with a mechanical stirrer, thermometer and a reflux condenser. Add acetone
30 (240mL) and heat the mixture to reflux for about 20 hours. Cool the slurry to -15°C and isolate the solids by filtration on a coarse sintered glass frit funnel. Wash with ethyl acetate (50mL) and vacuum dry overnight to give
35 the title compound (26.1g, 93.7%); mp 197.5-199.5°C.

XRPD: Table 8

Table 8

	D-Space, Angstroms	Intensity, I/I ₀ , %
5	11.75	35
	7.23	35
	6.24	60
	5.89	40
10	5.02	20
	4.94	30
	4.83	100
	4.44	30
	3.93	75
15	3.83	20
	3.77	85
	3.71	25
	3.62	30
20	3.32	25
	3.31	20

Example 8-Conversion of Form IV into Form I

25 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-
hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride
(Form I)

Place 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-
 30 hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride
 hydrate (Form IV) (54.35g, 0.0970mol, having 4% water
 present) in a pressure bottle along with water (4.16g) and
 acetone (38.1g). Seal the bottle tightly and heat to
 approximately 80°C. Cool to less than 60°C, filter through
 35 filter aid in a coarse sintered glass funnel and rinse the
 filter cake with acetone (32.4g). Place acetone (215g) in
 a 1L three necked flask fitted with a mechanical stirrer,
 thermometer, a reflux condenser and containing a small

-30-

amount of Form I crystals and heat to reflux. Add a portion of the acetone/water solution of 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -
5 dimethylbenzeneacetic acid hydrochloride hydrate (Form IV) (47.65g) to the refluxing acetone over about 10 minutes. Slowly add ethyl acetate (157.5g) over 45 minutes then add the remaining portion of the acetone/water solution of 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-
10 hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride hydrate (Form IV), rinsed in with about 20mL of acetone. Add additional ethyl acetate (157.5g) over 45 minutes to 1 hour, maintaining the slurry at reflux. Stir for 15 minutes, cool to -15°C and vacuum filter the white solid on
15 a 350mL coarse sintered glass funnel. Wash the solids with ethyl acetate (2X50mL) and vacuum dry overnight to give the title compound (50.36g, 97%); mp 198-199.5°C.

XRPD: Table 9

20

25

30

35

-31-

Table 9

	D-Space, Angstroms	Intensity, I/I ₀ , %
5	14.89	20
	11.85	20
	7.30	20
	6.28	70
10	5.91	25
	5.55	20
	5.05	25
	4.96	55
	4.85	100
15	4.57	45
	4.45	55
	3.94	45
	3.89	20
20	3.84	20
	3.78	60
	3.72	35
	3.63	20
25	3.07	20
	3.04	20
	2.45	20

30

35

The polymorphic and pseudomorphic 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride compounds of this invention are useful as antihistamines, antiallergy agents and bronchodilators and may be administered alone or with suitable pharmaceutical carriers, and can be in solid or liquid form such as, tablets, capsules, powders, solutions, suspensions or emulsions.

10

The polymorphic and pseudomorphic 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride compounds of this invention can be administered orally, parenterally, for example, subcutaneously, intravenously, intramuscularly, intraperitoneally, by intranasal instillation or by application to mucous membranes, such as, that of the nose, throat and bronchial tubes, for example, in an aerosol spray containing small particles of a compound of this invention in a spray or dry powder form.

The quantity of polymorphic or pseudomorphic 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride compound administered will vary depending on the patient and the mode of administration and can be any effective amount. The quantity of polymorphic or pseudomorphic 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride compound administered may vary over a wide range to provide in a unit dosage an effective amount of from about 0.01 to 20 mg/kg of body weight of the patient per day to achieve the desired effect. For example, the desired antihistamine, antiallergy and bronchodilator effects can be obtained by consumption of a unit dosage form such as a tablet containing 1 to 500 mg of a polymorphic or pseudomorphic 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-

35

-33-

hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride compound of this invention taken 1 to 4 times daily.

5 The solid unit dosage forms can be of the conventional type. Thus, the solid form can be a capsule which can be the ordinary gelatin type containing a polymorphic or pseudomorphic 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid
10 hydrochloride compound of this invention and a carrier, for example, lubricants and inert fillers such as lactose, sucrose or cornstarch. In another embodiment the polymorphic or pseudomorphic 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -
15 dimethylbenzeneacetic acid hydrochloride compound is tableted with conventional tablet bases such as lactose, sucrose or cornstarch or gelatin, disintegrating agents such as cornstarch, potato starch or alginic acid, and a lubricant such as stearic acid or magnesium stearate.

20 The polymorphic or pseudomorphic 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride compounds of this invention may also be administered in injectable dosages by
25 solution or suspension of the compounds in a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid such as water and oils, with or without the addition of a surfactant and other pharmaceutically acceptable adjuvants. Illustrative
30 of oils there can be mentioned those of petroleum, animal, vegetable or synthetic origin, for example, peanut oil, soybean oil or mineral oil. In general, water, saline, aqueous dextrose and related sugar solutions and glycols such as propylene glycol or polyethylene glycol are
35 preferred liquid carriers, particularly for injectable solutions.

-34-

For use as aerosols the compounds of this invention in solution or suspension may be packaged in a pressurized aerosol container together with suitable propellants, for example, hydrocarbon propellants such as, propane, butane or isobutane with the usual adjuvants as may be administered in a non-pressurized form such as in a nebulizer or atomizer.

10 The term patient as used herein is taken to mean warm blooded animals, birds, mammals, for example, humans, cats, dogs, horses, sheep, bovine cows, pigs, lambs, rats, mice and guinea pigs.

15

20

25

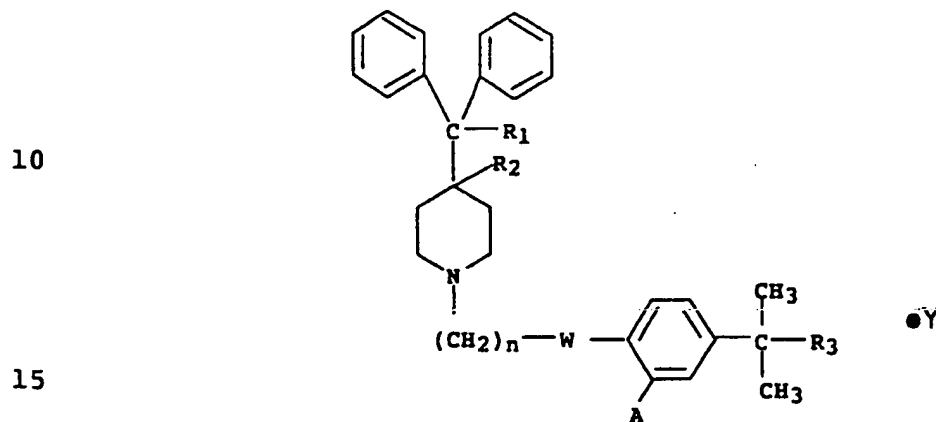
30

35

-35-

WHAT IS CLAIMED IS:

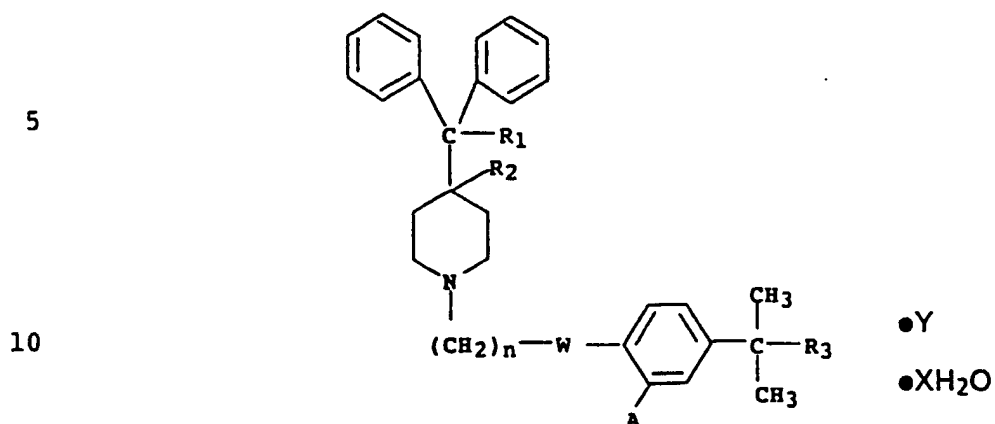
1. A process for preparing a compound of the formula



wherein

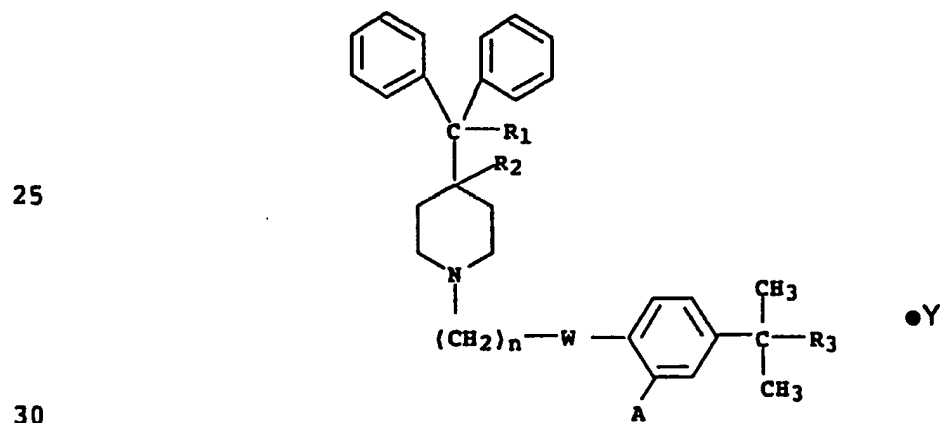
- 20 R_1 represents hydrogen or hydroxy;
 R_2 represents hydrogen; or
 R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2 ;
 n is an integer of from 1 to 5;
 R_3 is $-\text{CH}_2\text{OH}$, $-\text{COOH}$ or $-\text{COOalkyl}$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or
 25 branched;
 W is $-\text{CH}(\text{OH})-$ or $-\text{C}(=\text{O})-$;
 A is hydrogen or hydroxy;
 Y is a pharmaceutically acceptable acid; and
 30 the individual optical isomers thereof,
 comprising subjecting a compound of the formula

35



and the individual optical isomers thereof, wherein R_1 , R_2 ,
15 R_3 , n , W , A and Y are defined above and X is a number
ranging essentially from 0.10 to 5 to an azeotropic
distillation.

20 2. A process for preparing a compound of the formula



wherein

R₁ represents hydrogen or hydroxy;

R₂ represents hydrogen; or

35 R₁ and R₂ taken together form a second bond between the carbon atoms bearing R₁ and R₂;
n is an integer of from 1 to 5;

-37-

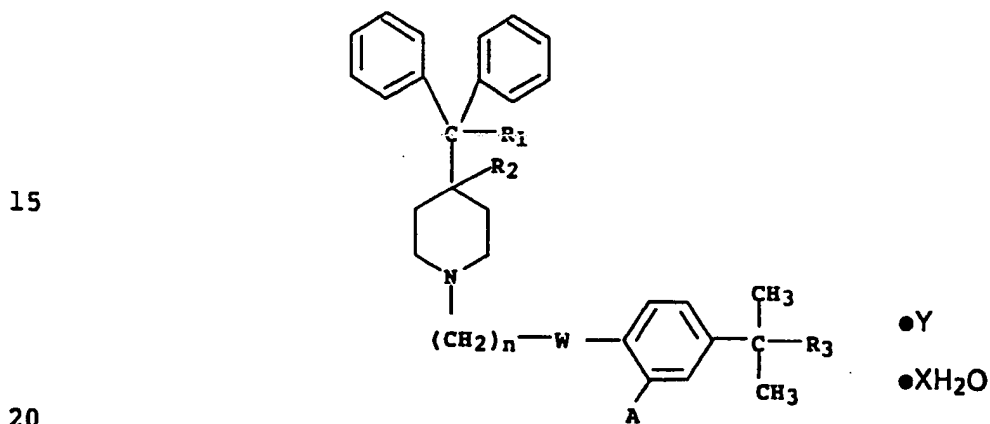
R_3 is $-\text{CH}_2\text{OH}$, $-\text{COOH}$ or $-\text{COOalkyl}$ wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

5 W is $-\text{CH}(\text{OH})-$ or $-\text{C}(=\text{O})-$;

A is hydrogen or hydroxy;

Y is a pharmaceutically acceptable acid; and
the individual optical isomers thereof,
comprising subjecting a compound of the formula

10



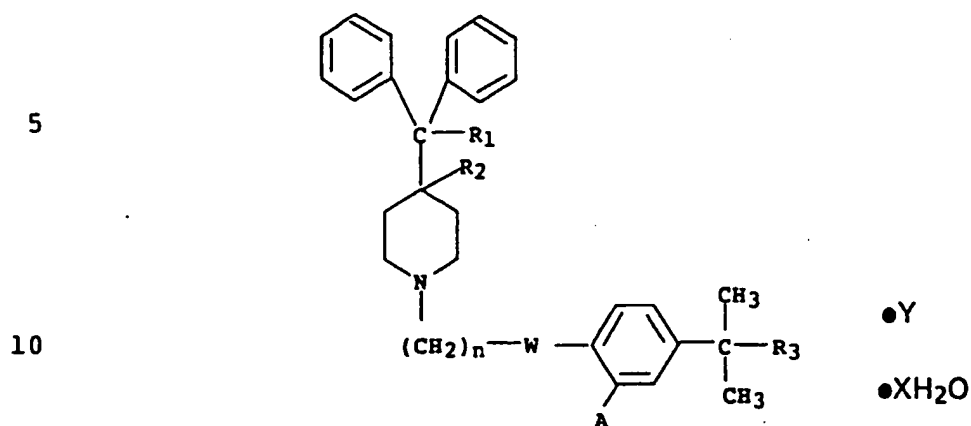
and the individual optical isomers thereof, wherein R_1 , R_2 , R_3 , n , W , A and Y are defined above and X is a number ranging essentially from 0.10 to 5 to a water-minimizing
25 recrystallization.

3. A process for preparing a compound of the formula

30

35

-38-



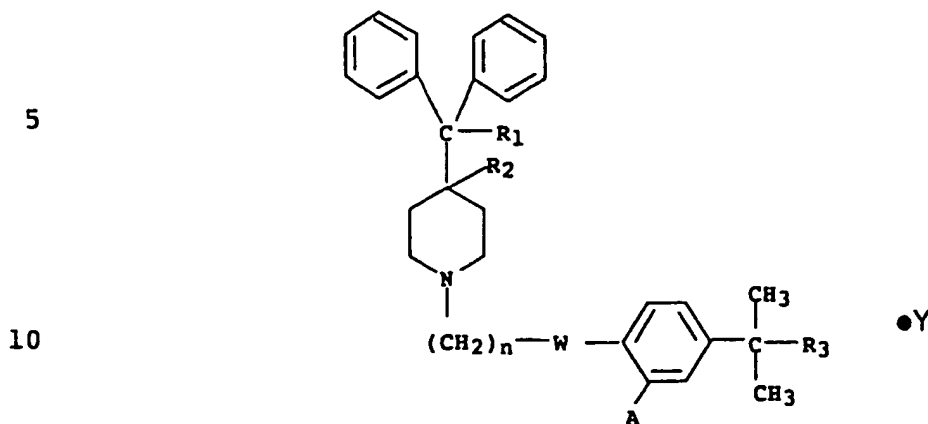
wherein

- 15 R₁ represents hydrogen or hydroxy;
 R₂ represents hydrogen; or
 R₁ and R₂ taken together form a second bond between the
 carbon atoms bearing R₁ and R₂;
 n is an integer of from 1 to 5;
- 20 R₃ is -CH₂OH, -COOH or -COOalkyl wherein the alkyl
 moiety has from 1 to 6 carbon atoms and is straight or
 branched;
 W is -CH(OH)- or -C(=O)-;
- 25 A is hydrogen or hydroxy;
 Y is a pharmaceutically acceptable acid;
 X is a number ranging essentially from 0.1 to 5; and
 the individual optical isomers thereof,
- comprising subjecting a compound of the formula

30

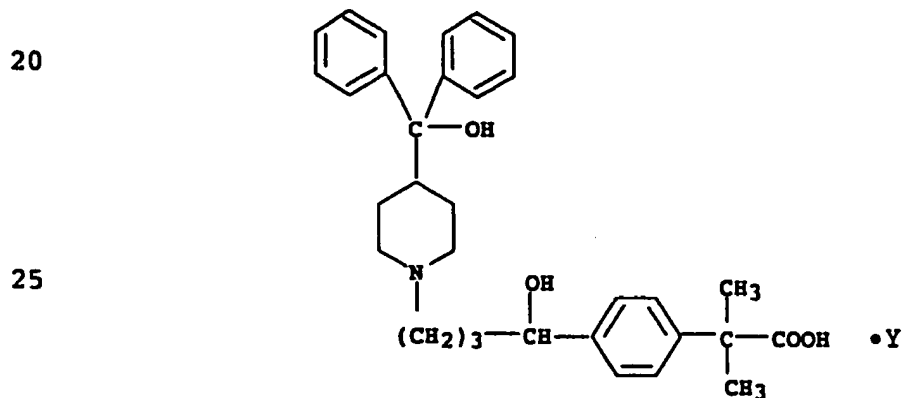
35

-39-



and the individual optical isomers thereof wherein R₁, R₂,
 15 R₃, n, A, W and Y are as defined above, to an aqueous
 recrystallization.

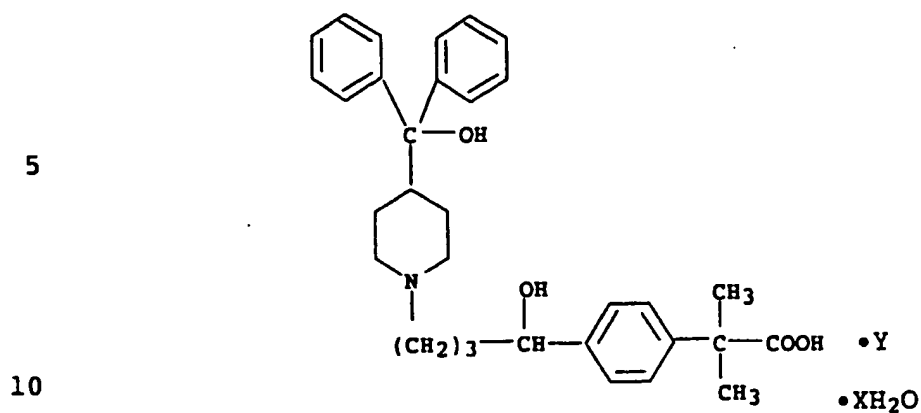
4. A process for preparing a compound of the formula



30 and the individual optical isomers thereof, wherein Y is a
 pharmaceutically acceptable acid, comprising subjecting a
 compound of the formula

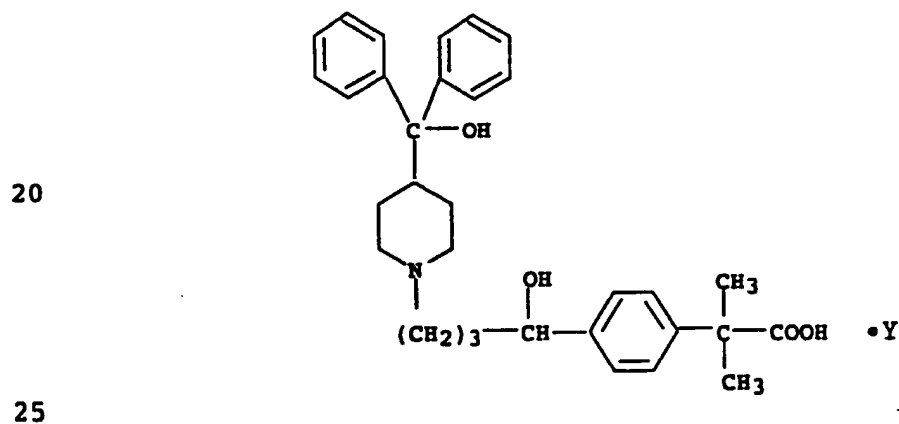
35

-40-



wherein Y is as defined above and X is a number ranging essentially from 0.10 to 5 to an azeotropic distillation.

15 5. A process for preparing a compound of the formula

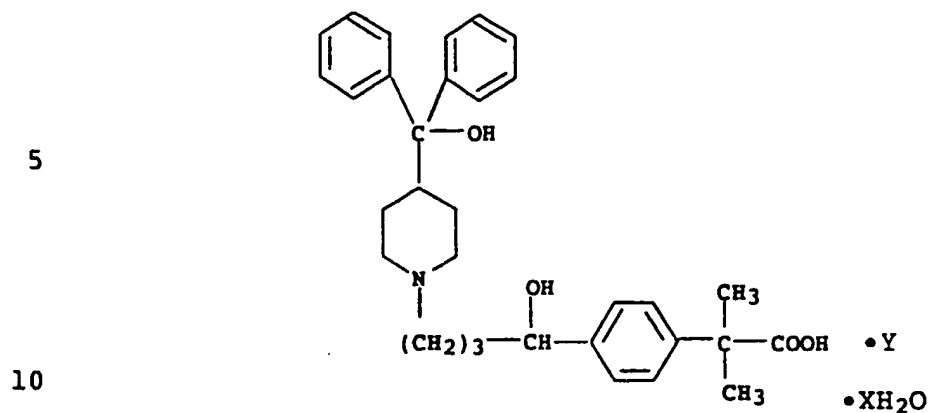


and the individual optical isomers thereof, wherein Y is a pharmaceutically acceptable acid, comprising subjecting a compound of the formula

30

35

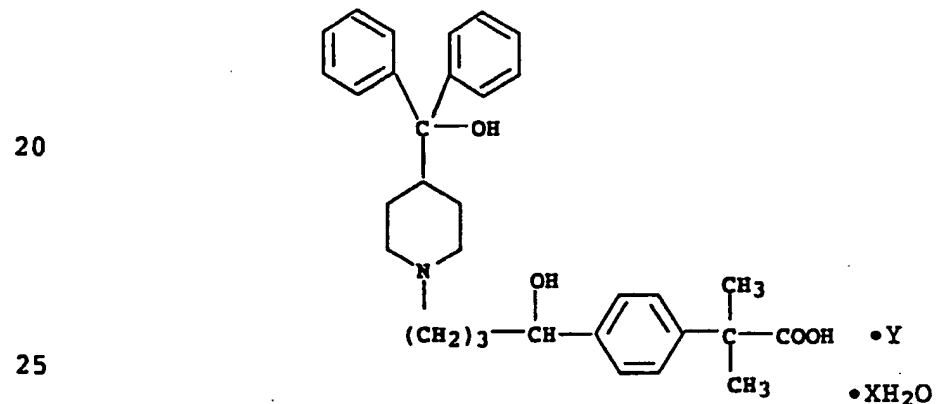
-41-



wherein Y is as defined above and X is a number ranging essentially from 0.10 to 5 to a water-minimizing recrystallization.

15

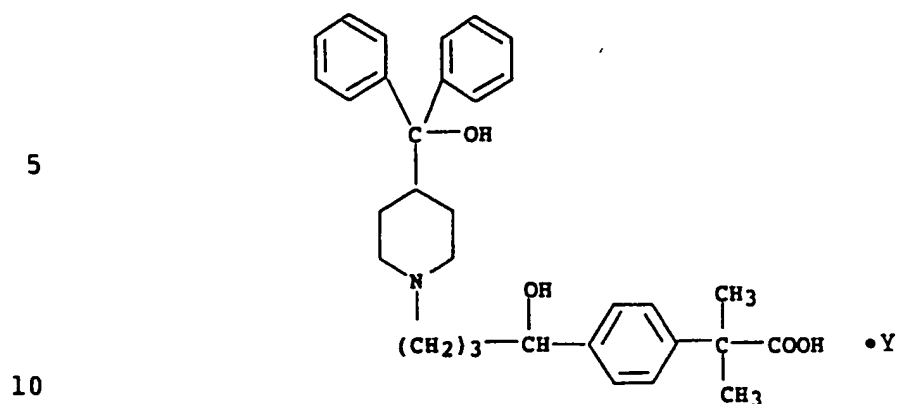
6. A process for preparing a compound of the formula



and the individual optical isomers thereof, wherein Y is a pharmaceutically acceptable acid and X is a number ranging essentially from 0.10 to 5, comprising subjecting a compound of the formula

35

-42-



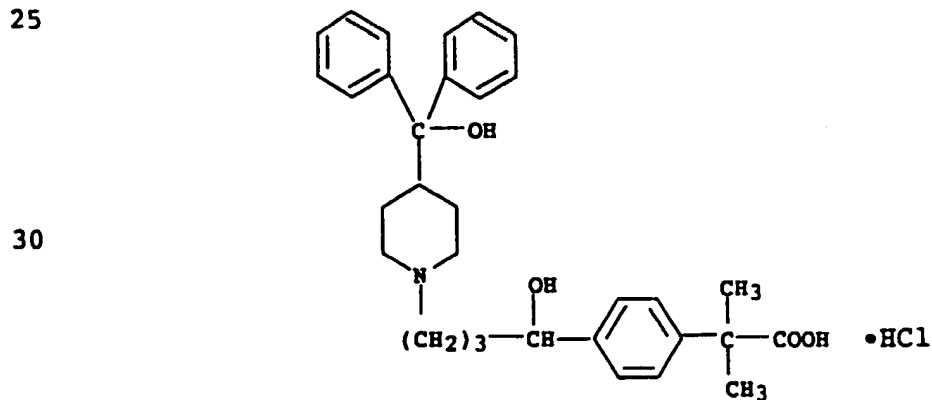
wherein Y is as defined above to an aqueous recrystallization.

15 7. A process according to Claim 4, Claim 5 or Claim 6 wherein Y is HCl.

20 8. A process according to Claim 7 wherein x is a number ranging from 1 to 4.

9. A process according to Claim 8 wherein x is a number ranging from 2 to 3.

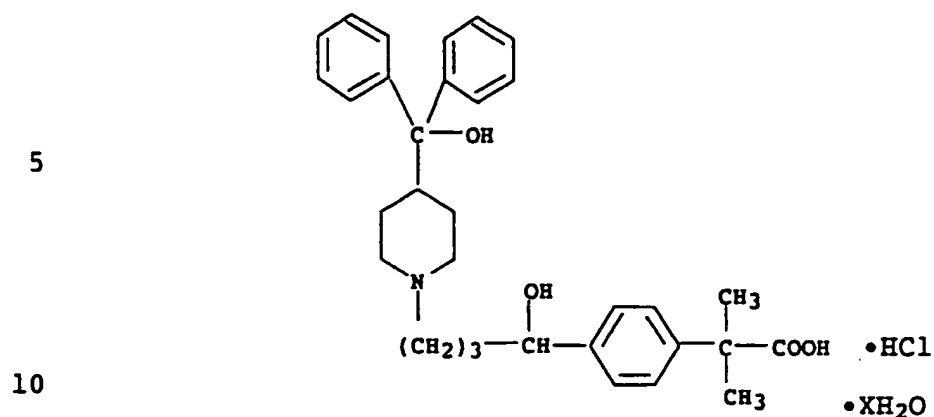
25 10. A compound of the formula



35 and the individual optical isomers thereof, formed by the process comprising the steps of:

a) treating a compound of the formula

-43-



wherein X is a number ranging from 0.1 to 5 and the individual optical isomers thereof, with a suitable solvent or solvent mixture;

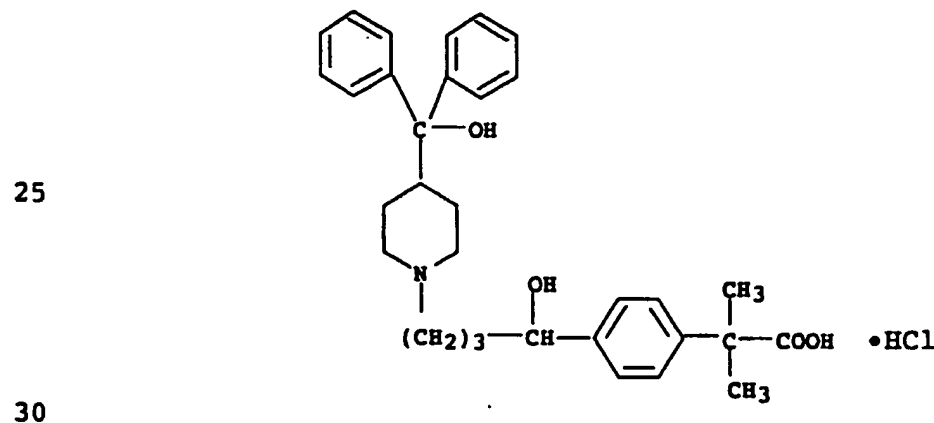
15

b) heating the mixture to a suitable temperature; and

c) cooling the mixture to complete crystallization.

20

11. A compound of the formula

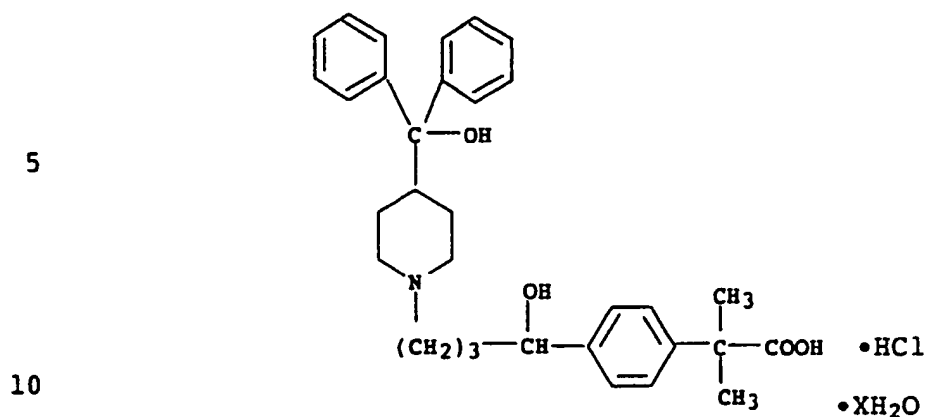


and the individual optical isomers thereof, formed by the process comprising the steps of:

a) treating a compound of the formula

35

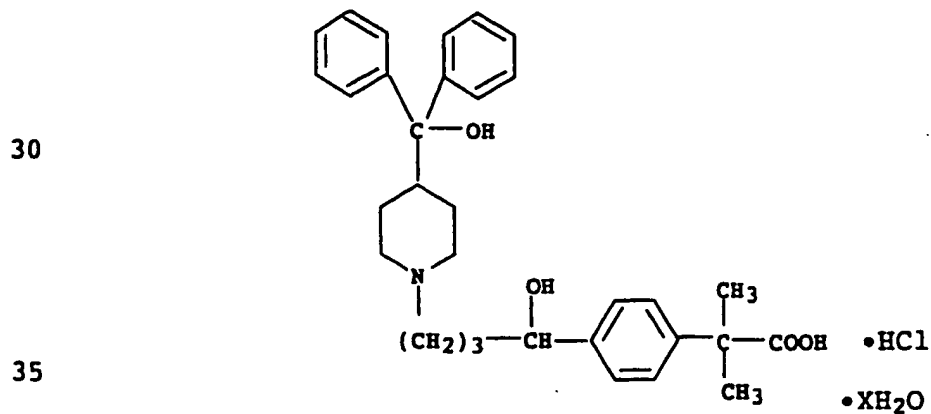
-44-



wherein X is a number ranging from 0.1 to 5 and the individual optical isomers thereof, with a suitable anhydrous solvent or solvent mixture in an amount sufficient to cause dissolution;

- b) heating the mixture to a suitable temperature.
- c) adding an additional volume of a suitable anhydrous solvent or solvent mixture in a quantity sufficient to initiate crystallization; and
- d) cooling the reaction mixture to complete crystallization.

12. A compound of the formula

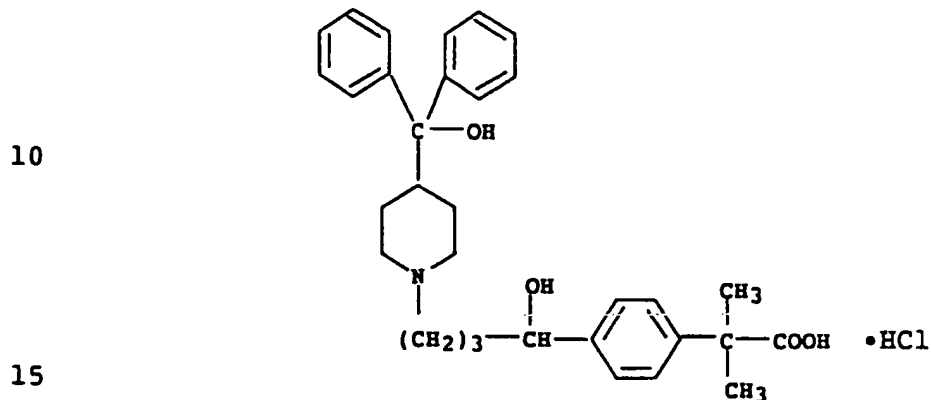


-45-

wherein X is a number ranging from 0.1 to 5 and the individual optical isomers thereof, formed by the process comprising the steps of:

5

a) treating a compound of the formula



and the individual optical isomers thereof with a suitable solvent;

20

b) heating the mixture to a suitable temperature; and

c) cooling the mixture to initiate crystallization.

25

13. Form I anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α,α-dimethylbenzeneacetic acid hydrochloride.

30

14. Form II hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α,α-dimethylbenzeneacetic acid hydrochloride.

35

15. Form III anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α,α-dimethylbenzeneacetic acid hydrochloride.

16. Form IV hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride.

5

17. A pharmaceutical composition comprising an effective antiallergic amount of a compound of Claim 13 in admixture or otherwise in association with an inert carrier.

10

18. A pharmaceutical composition comprising an effective antiallergic amount of a compound of Claim 14 in admixture or otherwise in association with an inert carrier.

15

19. A pharmaceutical composition comprising an effective antiallergic amount of a compound of Claim 15 in admixture or otherwise in association with an inert carrier.

20

20. A pharmaceutical composition comprising an effective antiallergic amount of a compound of Claim 16 in admixture or otherwise in association with an inert carrier.

25

21. A method of treating allergic reactions in a patient in need thereof which comprises administering to said patient an anti-allergically effective amount of a compound of claim 13.

30

22. A method of treating allergic reactions in a patient in need thereof which comprises administering to said patient an anti-allergically effective amount of a compound of claim 14.

35

23. A method of treating allergic reactions in a patient in need thereof which comprises administering to

-47-

said patient an anti-allergically effective amount of a compound of claim 15.

5 24. A method of treating allergic reactions in a patient in need thereof which comprises administering to said patient an anti-allergically effective amount of a compound of claim 16.

10 25. A process for preparing the Form I anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride which comprises subjecting Form II hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -
15 dimethylbenzeneacetic acid hydrochloride to a water-minimizing recrystallization.

26. A process according to Claim 25 wherein suitable anhydrous solvents or solvent mixtures which are sufficient
20 to cause dissolution are acetone and water and a suitable anhydrous antisolvent is ethyl acetate.

27. A process for preparing the Form I anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride which
25 comprises subjecting Form II hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride to an azeotropic distillation.

30 28. A process according to claim 27 wherein suitable solvents or solvent mixtures which are sufficient to cause dissolution are methanol, acetone/water and methyl ethyl ketone/water and a suitable anhydrous antisolvent is methyl
35 ethyl ketone.

29. A process for preparing the Form I anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-

5 α,α -dimethylbenzeneacetic acid hydrochloride which comprises subjecting Form III anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride to a crystal digestion.

10 30. A process for preparing the Form I anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride which comprises subjecting Form IV hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride to a water-minimizing recrystallization.

15

31. A process according to Claim 30 wherein suitable anhydrous solvents or solvent mixtures which are sufficient to cause dissolution are acetone and water and a suitable anhydrous antisolvent is ethyl acetate.

20

32. A process for preparing the Form I anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride which comprises subjecting Form IV hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride to an azeotropic distillation.

25

33. A process according to claim 32 wherein suitable solvents or solvent mixtures which are sufficient to cause dissolution are methanol, acetone/water and methyl ethyl ketone/water and a suitable anhydrous antisolvent is methyl ethyl ketone.

30

34. A process for preparing the Form II hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride which comprises:

35

-49-

- 5 a) reacting ethyl 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylbenzeneacetate hydrochloride with an appropriate reducing agent in a suitable solvent;
- b) acidifying with hydrochloric acid; and
- 10 c) adding water over a period of time ranging from 1 minute to 45 minutes at a temperature range of about -20°C to 50°C .
- 15 35. A process according to claim 34 wherein the water is added over a period of time ranging from 10 minutes to 30 minutes at a temperature range of about 0°C to 40°C .
- 20 36. A process according to claim 35 wherein the water is added over a period of time ranging from 10 minutes to 30 minutes at a temperature range of about 20°C to 40°C .
- 25 37. A process for preparing the Form II hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride which comprises:
- 30 a) reacting ethyl 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylbenzeneacetate with an appropriate reducing agent in a suitable solvent;
- b) acidifying with hydrochloric acid; and
- 35 c) adding water over a period of time ranging from 1 minute to 45 minutes at a temperature range of about -20°C to 50°C .

38. A process according to claim 37 wherein the water is added over a period of time ranging from 10 minutes to 30 minutes at a temperature range of about 0°C to 40°C.

5

39. A process according to claim 38 wherein the water is added over a period of time ranging from 10 minutes to 30 minutes at a temperature range of about 20°C to 40°C.

10

40. A process for preparing the Form II hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride which comprises subjecting Form I anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride to an aqueous recrystallization.

15

41. A process for preparing the Form III anhydrous 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride which comprises subjecting Form II hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride to a water-minimizing recrystallization.

25

42. A process for preparing the Form IV hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride which comprises:

30

a) reacting ethyl 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylbenzeneacetate hydrochloride with an appropriate reducing agent in a suitable solvent;

35

b) acidifying with hydrochloric acid; and

-51-

- c) adding water over a period of time ranging from 30 minutes to 24 hours at a temperature range of about 0°C to 50°C.

5

43. A process according to claim 42 wherein the water is added over a period of time ranging from 1 hour to 12 hours at a temperature range of about 10°C to 40°C.

10

44. A process according to claim 43 wherein the water is added over a period of time ranging from 2 hours to 8 hours at a temperature range of about 20°C to 40°C.

45. A process for preparing the Form IV hydrated 4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid hydrochloride which comprises:

20

- a) reacting ethyl 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-oxobutyl]- α,α -dimethylbenzeneacetate with an appropriate reducing agent in a suitable solvent;

25

- b) acidifying with hydrochloric acid; and

- c) adding water over a period of time ranging from 30 minutes to 24 hours at a temperature range of about 0°C to 50°C.

30

46. A process according to claim 45 wherein the water is added over a period of time ranging from 1 hour to 12 hours at a temperature range of about 10°C to 40°C.

47. A process according to claim 46 wherein the water is added over a period of time ranging from 2 hours to 8 hours at a temperature range of about 20°C to 40°C.

35

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/04942

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/22 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 21156 (MERRELL DOW PHARM. INC.) 28 October 1993 Title compound of step e on page 34 see page 1, line 12 ---	10-24
X	US,A,4 285 957 (CARR) 25 August 1981 Examples 1-3 ---	10-24
X	US,A,4 254 129 (CARR) 3 March 1981 cited in the application Examples 1-3 ---	10-24
A	US,A,4 285 958 (CARR) 25 August 1981 cited in the application see claim 1 --- -/-	10-24

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

10 August 1995

Date of mailing of the international search report

- 6. 09 95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Gettins, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 95/04942

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 254 130 (CARR) 3 March 1981 cited in the application see claim 1 ---	10-24
A	US,A,3 878 217 (CARR) 15 April 1975 see claim 1 -----	10-24

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/04942

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9321156	28-10-93	AU-B-	3797393	18-11-93
		EP-A-	0635004	25-01-95
		FI-A-	944713	02-12-94
		NO-A-	943794	09-12-94
		ZA-A-	9302454	20-10-93

US-A-4285957	25-08-81	US-A-	4254129	03-03-81
		AT-B-	376208	25-10-84
		AU-B-	531146	11-08-83
		AU-A-	5501680	16-10-80
		BE-A-	882703	31-07-80
		CA-A-	1123438	11-05-82
		CH-A-	643245	30-05-84
		DE-A-	3007498	23-10-80
		FR-A, B	2453854	07-11-80
		GB-A, B	2048258	10-12-80
		JP-B-	1032823	10-07-89
		JP-C-	1555761	23-04-90
		JP-A-	55141469	05-11-80
		NL-A, B, C	8000754	14-10-80
		SE-B-	448726	16-03-87
		SE-A-	8002634	11-10-80

US-A-4254129	03-03-81	AT-B-	376208	25-10-84
		AU-B-	531146	11-08-83
		AU-A-	5501680	16-10-80
		BE-A-	882703	31-07-80
		CA-A-	1123438	11-05-82
		CH-A-	643245	30-05-84
		DE-A-	3007498	23-10-80
		FR-A, B	2453854	07-11-80
		GB-A, B	2048258	10-12-80
		JP-B-	1032823	10-07-89
		JP-C-	1555761	23-04-90
		JP-A-	55141469	05-11-80
		NL-A, B, C	8000754	14-10-80
		SE-B-	448726	16-03-87
		SE-A-	8002634	11-10-80
		US-A-	4285957	25-08-81

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/04942

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4285958	25-08-81	US-A- 4254130	03-03-81
		AT-B- 376207	25-10-84
		AU-B- 536463	10-05-84
		AU-A- 5501880	16-10-80
		BE-A- 882704	31-07-80
		CA-A- 1123439	11-05-82
		CH-A- 648019	28-02-85
		DE-A- 3005948	30-10-80
		FR-A, B 2453853	07-11-80
		GB-A, B 2048258	10-12-80
		JP-A- 55139360	31-10-80
		NL-A, B, C 8000762	14-10-80
		SE-B- 448727	16-03-87
		SE-A- 8002635	11-10-80
US-A-4254130	03-03-81	AT-B- 376207	25-10-84
		AU-B- 536463	10-05-84
		AU-A- 5501880	16-10-80
		BE-A- 882704	31-07-80
		CA-A- 1123439	11-05-82
		CH-A- 648019	28-02-85
		DE-A- 3005948	30-10-80
		FR-A, B 2453853	07-11-80
		GB-A, B 2048258	10-12-80
		JP-A- 55139360	31-10-80
		NL-A, B, C 8000762	14-10-80
		SE-B- 448727	16-03-87
		SE-A- 8002635	11-10-80
		US-A- 4285958	25-08-81
US-A-3878217	15-04-75	AT-B- 321917	25-04-75
		AT-B- 323742	25-07-75
		AU-B- 467361	27-11-75
		AU-A- 4989372	13-06-74
		BE-A- 794597	16-05-73
		CA-A- 978946	02-12-75
		CH-A- 593259	30-11-77
		CH-A- 587820	13-05-77
		DE-A- 2303306	02-08-73
		FR-A, B 2181690	07-12-73

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 95/04942

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-3878217		GB-A- 1413138	05-11-75
		JP-C- 840584	20-01-77
		JP-A- 48085578	13-11-73
		JP-B- 51015035	13-05-76
		LU-A- 66916	27-07-73
		NL-A- 7300873	31-07-73
		SE-B- 382058	12-01-76
<hr/>			